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Müller et al.

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(54) **STABLE CRYSTALLINE (6R)-TETRAHYDROFOLIC ACID**

GB 1379532 1/1975
WO 88/08844 11/1988

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OTHER PUBLICATIONS

CRC Handbook of Chemistry and Physics, David R. Lide, Ph.D., 1994—1995 75th Edition.

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The role of pH change caused by the addition of water-miscible organic solvents in the destabilization of an enzyme, S. Shubhada et al., *Enzyme Microb. Technol.*, 1995, vol. 17, Apr. pp. 331–335.

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

Journal of Pharmaceutical and Biomedical Analysis. Variation of Acidity Constants and pH Values of Some Organic Acids in Water/2-Propanol Mixtures with Solvent Composition. Effect of Preferential Solvation, *Analytica Chimia Acta*, 302, 109–119 (1995).

(21) Appl. No.: **09/755,072**

Reference from www.emscience.com/chromsite/hplcfaqs-answers.htm, FAQ's/HPLC.

(22) Filed: **Jan. 8, 2001**

(65) **Prior Publication Data**

Reference from www.polyurethane.org/standards-test-methods/poly-raw-materials/article4.html, Apparent pH of Polyether Polyols—A comparison of Methods M.A. Carey et al.

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Related U.S. Application Data

(62) Division of application No. 09/013,266, filed on Jan. 26, 1998, now Pat. No. 6,271,374, which is a continuation of application No. 08/437,716, filed on May 9, 1995, now abandoned.

Hawley, Gessner, "The Condensed Chemical Dictionary", 1977, Van Nostrand, New York, pp. 54–55 and 666.*

(30) **Foreign Application Priority Data**

May 9, 1994 (CH) 1442/94

Pauling, Linus, "General Chemistry, 2nd Ed.", 1953, Freeman, San Francisco, p. 22.*

(51) **Int. Cl.**⁷ **C07D 475/04**; A61K 31/519

Ford, Richard A., "The Chemist's Companion", John Wiley's & Sons, New York, 1972, p. 56.*

(52) **U.S. Cl.** **514/249**; 544/258

Carlson et al., "Antitumour Effects of Pure Diastereoisomers of . . .", *Bio. Pharm.*, 50:9, 1347–1351, 1995.

(58) **Field of Search** 514/249; 544/258

"Dictionary of Organic Compounds", no author listed, 6th Ed., vol. 4, Chapman & Hall, New York, 1996, p. 3235.*

Stout, G.H. and Jensen, L.H., "Practical X-ray Crystallography", Macmillan New York, 1970, p. 66.*

(56) **References Cited**

* cited by examiner

U.S. PATENT DOCUMENTS

5,006,655 A	4/1991	Müller et al.	544/258
5,324,836 A *	6/1994	Müller et al.	544/258
5,350,851 A *	9/1994	Bailey et al.	544/258
5,489,684 A *	2/1996	Jequier et al.	544/258
5,698,693 A *	12/1997	Fitzhugh et al.	544/258
6,465,404 B2	10/2002	Scriven, II et al.	

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FOREIGN PATENT DOCUMENTS

DE	2323124	11/1973
EP	0432441	6/1991
EP	0495204	7/1992
EP	0600460	6/1994

(57) **ABSTRACT**

Pure and extremely stable crystalline (6R)-tetrahydrofolic acids, absolutely inert even when exposed to air and elevated temperature without stabilizers being added, are prepared by a crystallization process at a pH of ≥ 2 .

16 Claims, No Drawings